Pharm World Sci (2006) 28:159–162
DOI 10.1007/s11096-006-9030-x

CASE REPORT

Total body topical 5-fluorouracil for extensive non-melanoma skin cancer

Serge van Ruth · Frank G.A. Jansman · Cornelis J. Sanders

Received: 14 March 2006 / Accepted: 16 May 2006 / Published online: 27 September 2006

Abstract
Background Topical 5-fluorouracil 5% cream is one of the treatment modalities for non-melanoma skin cancer (NMSC). There is a lack of suitable therapies to treat patients with extensive NMSC. In this paper we report two patients with extensive NMSC treated by total body application of topical 5-fluorouracil 5% cream.
Observations Topical 5-fluorouracil 5% cream was applied twice daily to the total body, including normal appearing skin. During the treatment, weekly blood samples were taken for measurement of 5-fluorouracil levels. All samples showed a 5-fluorouracil level less than the detection level of 10 μg/l. Total body 5-fluorouracil 5% cream was shown to be an effective treatment in our patients; the majority of lesions cleared in both patients.
Conclusions In conclusion, total body topical 5-fluorouracil 5% cream application was successful in two patients with extensive NMSC. No detectable serum level of 5-fluorouracil could be determined. Pain and secondary infections were important side effects in our patients. However, in patients with extensive NMSC this treatment may be considered.

Keywords Basal cell carcinoma · Cancer · Non-melanoma skin cancer · Systemic absorption · Topical 5-fluorouracil

Impact of this article on practice

- Total body topical 5-fluorouracil cream can be considered in the treatment of extensive non-melanoma skin cancer.
- Total body topical 5-fluorouracil is associated with minimal systemic absorption. Further research is warranted to this treatment in non-melanoma skin cancer.

Introduction

There are several treatment modalities for non-melanoma skin cancer (NMSC) [1]. Surgery, cryotherapy, topical 5-fluorouracil and radiation therapy are the mainstay of treatment. Newer modalities are photodynamic therapy (PDT) and imiquimod. Treatment of thin (superficial) basal cell carcinomas with topical 5-fluorouracil is widely accepted despite the absence of published 5-year cure rates. The producer advices to treat a limited body surface area (approximately 500 cm^2) to reduce the risk of systemic absorption. From the doctors perspective there are cases when treating larger areas or even total body

S. van Ruth · C. J. Sanders
Department of Dermatology and Allergology, University Medical Centre Utrecht, Utrecht, The Netherlands

F. G.A. Jansman (✉)
Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration (GUIDE), Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands
e-mail: f.g.a.jansman@isala.nl

F. G.A. Jansman
Department of Clinical Pharmacy, Isala klinieken, Zwolle, The Netherlands

application is desirable, because there is a lack of suitable therapies to treat patients with extensive NMSC. In this paper we report two patients with extensive NMSC treated by total body application of topical 5-fluorouracil 5% cream. Total body application was chosen in order to treat both obvious carcinomas and minimal or subclinical NMSC.

Case report one

This case represents a 73-year-old man with a past medical history of ichthyosis vulgaris and mycosis fungoides. He had been treated before with topical nitrogen mustard application, topical steroids, UVB therapy and, for the past 10 years, with photo chemotherapy (PUVA) in order to control the mycosis fungoides. He received a cumulative dose of 8300 J/cm^2 which is far beyond the general accepted maximum cumulative dose of 2000–4000 J/cm^2. In recent months the patient developed more than one hundred epithelial tumours at his atrophic skin. Histopathology of several skin biopsies showed mainly superficial basal cell carcinomas, several actinic keratoses, occasional squamous cell carcinomas and mycosis fungoides lesions. His PUVA therapy was stopped and he received acitretin 20 mg daily and topical steroids.

Topical 5-fluorouracil 5% cream (Efudix®) was applied, wearing gloves, twice weekly to the total body on an outpatient clinic base, using 20 g per application. Inactive ingredients were methyl- and propyl-parahydroxybenzoate, propylene glycol (1520), polysorbate 60, stearylalcohol, white paraffin and purified water. The treatment period was 6 weeks. Blood samples were taken before, 30-60-90-120-240 min after and 24 h after application in order to measure the 5-fluorouracil level. During treatment analgesics were administered to reduce pain. After 6 weeks erosions had developed and topical 5-fluorouracl 5% cream application was stopped. He developed shaking chills, fever and a staphyloccal aureus sepsis. He was admitted to hospital. At that time no leucopenia was observed. There was a full recovery after 14 days administration of flucloxacillin intravenously.

Measurement of 5-fluorouracil blood levels was performed by a validated reversed-phase high-performance liquid chromatographic analysis according to reference [2]. The detection level was 10 μg/l. The minimal therapeutic level was 25 μg/l. All samples showed a 5-fluorouracil level less than 10 μg/l.

No epithelial tumours were present several months later. After a follow-up of 3 years he has developed localized actinic keratoses and basal cell carcinomas, controlled by topical 5-fluorouracil 5% cream or excision. His mycosis fungoides is managed by topical application of nitrogen mustard ointment.

Case report two

A 30-year-old man with nevoid basal cell carcinoma syndrome presented with progressive basal cell carcinomas, both nodular and superficial. His past medical history disclosed an inguinal hernia and repeated extirpation of jaw cysts. Previous therapy of basal cell carcinomas included surgical excision, cryotherapy and topical 5-fluorouracil 5% cream. In order to slow down the progress of developing new basal cell carcinomas, acitretin in a dose of 35 mg daily had been taken for 5 years. More than 70 basal cell carcinomas were diagnosed and the patient was admitted to the hospital (Fig. 1). The majority of the basal cell carcinomas were of the superficial type and about 10% were nodular types, mainly located on the neck and arms.

Topical 5-fluorouracil 5% cream was applied twice daily to the total body, including normal appearing skin. The total quantity of topical 5-fluorouracil 5% cream used during admission was 400 g (13 g daily). During the treatment, weekly blood samples were taken for measurement of 5-fluorouracil levels. All samples showed a 5-fluorouracil level less than the detection level of 10 μg/l.

Some nodular basal cell carcinomas were treated with photodynamic therapy or excision. During the

Fig. 1 Before therapy

treatment, analgesics and antiseptics were prescribed and special attention was given to local wound dressings to prevent infection and alleviate pain. After 4 weeks of treatment the majority of lesions were eroded and therapy was stopped. Because of secondary infection, systemic antibiotics were administered (erythromycin 250 mg four daily for 2 weeks). A few days after discontinuation of the topical 5-fluorouracil 5% cream therapy, our patient could be discharged.

Six weeks after, patient was evaluated on the outpatient clinic. The majority of lesions had cleared (Fig. 2). Six months after starting therapy, patient is doing well without active epithelial tumours (Fig. 3).

Discussion

Topical 5-fluorouracil has been used widely for (pre) malignancies, such as actinic keratoses, superficial basal cell carcinomas and Bowen's disease [3, 4]. Less experience has been gained for treating squamous cell carcinomas [5]. There are different concentrations of topical 5-fluorouracil cream in use, but the majority of studies deals with topical 5-fluorouracil 5% cream. In the majority of people one or a few lesions are treated at the same time. In certain cases, however, patients exhibit extensive numbers of basal cell carcinomas for example in nevoid basal cell carcinoma syndrome, after total body radiation therapy or after repeated courses of PUVA. In those particular cases the restricted area that is advised for topical 5-fluorouracil 5% cream is a significant problem. Systemic administration of 5-fluorouracil would be an option in those cases, however intensive topical treatment for widespread NMSC seems more attractable [6]. To our knowledge this is the first paper reporting total body topical 5-fluorouracil 5% cream therapy.

Fig. 2 After 6 weeks of therapy

Total body 5-fluorouracil 5% cream was shown to be an effective treatment in our patients; the majority of lesions cleared in both patients. The first patient was treated twice weekly. Because the subsequent plasmaconcentrations indicated that systemic absorption was minimal, the second patient was treated more aggressively, i.e. twice daily.

In the literature there are a few reports dealing with topical 5-fluorouracil 5% cream in nevoid basal cell carcinomas, where (partial) unresponsiveness was noticed [7, 8]. Addition of cryotherapy has been suggested to improve the clearance of basal cell carcinomas and actinic keratoses[8, 9]. The addition of retinoids to 5-fluorouracil 5% cream has been reported in the treatment of disseminate actinic keratoses and was found to be highly effective [10]. The therapy in our both patients was highly effective for multiple superficial basal cell carcinomas, and even for squamous cell carcinomas. Several nodular basal cell carcinomas in our second patient were treated by excision or photodynamic therapy.

Analysis of blood samples showed, in our patients, that systemic absorption did not lead to detectable blood levels or systemic side effects. Pharmacokinetic evaluation by Levy et al. [11] showed that topical application results in a minimal systemic absorption (10%), however, absorption can be up to 75 times greater in diseased skin. Notwithstanding the limited systemic absorption, myocardial ischemia was reported by Rozenman et al. [12] and even life-threatening toxicity occurred in one patient, however this was the case in a dihydropyrimidine dehydrogenase deficient person [13].

An important side effect is irritation, especially in combination with the erosions that occur during treatment. Analgesics and the application of proper wound dressings resulted in an acceptable situation and did not alter the mobility of the patient. Our first patient developed a sepsis and admission was necessary. In order to prevent this side effect, our second patient was given prophylactic systemic antibiotics when impetiginisation was noticed. Known possible side effects of topical 5-fluorouracil therapy include local effects like irritation and infection, but also contact dermatitis and, as mentioned before, also systemic side effects have been reported in literature [12–14].

In conclusion, total body topical 5-fluorouracil 5% cream application was successful in two patients with

Fig. 3 After 6 months of therapy

extensive NMSC. No detectable serum level of 5-fluorouracil could be determined. Pain and secondary infections were important side effects in our patients. However, in patients with extensive NMSC this treatment may be considered.

References

1. Chakrabarty A, Geisse JK. Medical therapies for non-melanoma skin cancer. Clin Dermatol 2004;22(3):183–8.
2. Joulia JM, Pinguet F, Grosse PY, et al. Determination of 5-fluorouracil an its main metabolites in plasma by high-performance liquid chromatography: application to a pharmacokinetic study. J Chromatogr BBiomed Sci Appl 1997;692(2):427–35.
3. Reymann F. Treatment of basal cell carcinoma of the skin with 5-fluorouracil ointment. A 10-year follow-up study. Dermatologica 1979;158(50):368–72.
4. Tutrone WD, Saini R, Caglar S, Weinberg JM, Crespo J. Topical therapy for actinic keratoses, I: 5-fluorouracil and imiquimod. Cutis 2003;71(5):365–70.
5. Hamouda B, Jamila Z, Najet R, et al. Topical 5-fluorouracil to treat multiple or unresectable facial squamous cell carcinomas in xeroderma pigmentosum. J Am Acad Dermatol 2001;44(6):1054.
6. Cartei G, Cartei F, Interlandi G, et al. Oral 5-fluorouracil in squamous cell carcinoma of the skin in the aged. Am J Clin Oncol 2000;23(2):181–4.
7. Hazen PG, Taub SJ. Basal cell nevus syndrome. Unresponsiveness of early cutaneous lesions to topical 5-fluorouracil or dinitrochlorobenzene. Dermatologica 1984;168(6):287–9.
8. Tsuji T, Otake N, Nishimura M. Cryosurgery and topical fluorouracil: a treatment method for widespread basal cell epithelioma in basal cell nevus syndrome. J Dermatol 1993;20(8):507–13.
9. Jorizzo J, Weiss J, Furst K, VandePol C, Levy SF. Effect of a 1-week treatment with 0.5% topical fluorouracil on occurrence of actinic keratosis after cryosurgery. Arch Dermatol 2004;140:813–6.
10. Sander CA, Pfeiffer C, Kligman AM, et al. Chemotherapy for disseminated actinic keratoses with 5-fluorouracil and isotretinoin. J Am Acad Dermatol 1997;36:236–8.
11. Levy S, Furst K, Chern W. A pharmacokinetic evaluation of 0.5% and 5% fluorouracil topical cream in patients with actinic keratosis. Clin Ther 2001;23(6):908–20.
12. Rozenman Y, Gurewich J, Gotsman MS. Myocardial ischemia by topical use of 5-fluorouracil. Int J Cardiol 1995;49(3):282–3.
13. Johnson MR, Hageboutros A, Wang K, High L, Smith JF, Diasio RB. Life-threatening toxicity in a hihydropyrimidine dehydrogenase-deficient patient after treatment with topical 5-fluorouracil. Clin Cancer Res 1999;5(8):2006–11.
14. Farrar CW, Bell HK, King CM. Allergic contact dermatitis from propylene glycol in Efudix cream. Contact Dermatitis 2003;48(6):345.